IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of

BOTTAZZI et al.

Serial No. 09/555,473

Filed: February 26, 2002

Title: PHARMACEUTICAL COMPOSITIONS CONTAINING THE LONG PENTRAXIN PTX3

Atty Dkt. 2801-18
C# M#

Group Art Unit: 1644

Examiner: NOLAN

Date: August 1, 2003

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

RESPONSE/AMENDMENT/LETTER

This is a response/amendment/letter in the above-identified application and includes an attachment which is hereby incorporated by reference and the signature below serves as the signature to the attachment in the absence of any other signature thereon.

☐ **Correspondence Address Indication Form Attached.**

Fees are attached as calculated below:

Total effective claims after amendment **0** minus highest number previously paid for **20** (at least 20) = 0 x $ 18.00	$	0.00
Independent claims after amendment **0** minus highest number previously paid for **3** (at least 3) = 0 x $ 84.00	$	0.00
If proper multiple dependent claims now added for first time, add $280.00 (ignore improper)	$	0.00
Petition is hereby made to extend the current due date so as to cover the filing date of this paper and attachment(s) ($110.00/1 month; $410.00/2 months; $930.00/3 months)	$	0.00
Terminal disclaimer enclosed, add $ 110.00	$	0.00
☐ First/second submission after Final Rejection pursuant to 37 CFR 1.129(a) ($750.00) ☐ Please enter the previously unentered , filed ☐ Submission attached	$	0.00
Subtotal	$	**0.00**
Other: Response; Copies of Inositol (Vitamin B8) bluecrossmn.com; Temporal dissociation between lithium-induced changes...[biopsychiatry.com]; Folic Acid [suprahealth.com]; Choline Chloride (excerpt from Merck's website); Therapeutic Category and Biological Activity Index; ICH Harmonised Tripartite Guideline; Excerpts from Butterworths Medical Dictionary; Definition of Frequently Used Terms... Albany Molecular Research, Inc.		**0.00**
TOTAL FEE ENCLOSED	$	**0.00**

The Commissioner is hereby authorized to charge any deficiency, or credit any overpayment, in the fee(s) filed, or asserted to be filed, or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Account No. 14-1140. A duplicate copy of this sheet is attached.

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NIXON & VANDERHYE P.C.
By Atty: B. J. Sadoff, Reg. No. 36,663

Signature: B J Sadoff

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of

BOTTAZZI et al. Atty. Ref.: 2801-18

Appl. No. 09/555,473 Group: 1644

Filed: February 26, 2002 Examiner: NOLAN

For: PHARMACEUTICAL COMPOSITIONS CONTAINING THE LONG PENTRAXIN PTX3

* * * * * * * * * * *

August 1, 2003

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

RESPONSE

Responsive to the Official Action dated May 1, 2003, consideration of the following and the attached are requested.

Claims 17-19 are pending.

The pending claims require the inclusion of a pharmaceutically acceptable excipient.

One of ordinary skill in the art will appreciate that an "excipient" is "anything other that the drug substance in the dosage form", as noted in the attached copy of the ICH Harmonised Tripartite Guideline, Stability Testing of New Drugs Substances in Products Q1A R(2). The same is confirmed by the attached copy of Volume 3, No. 3 "Technical Reports" from Albany Molecular Research, Inc. "Definition of Frequently Used Terms

and Regulatory Affairs and Quality Assurance" by Steven W. Fordham and Gary M. Klee, copyright 1999. Finally, attached is a copy of page 628 from Butterworths Medical Dictionary Second Edition, McDonald Critchley, Editor–in-Chief, which notes under the entry "excipients" that "excipients must not have therapeutic action on their own...".

The Examiner has rejected claims 17-19 as allegedly being anticipated by Alles (Blood, Volume 84, No. 10 (November 15), 1994: pages 3483-3493) based on the specific disclosure at page 3485, first full paragraph, wherein the Examiner asserts the reference teaches "expressing the full-length human PTX3 protein in COS cells and incubated in DMEM and then isolating the protein in the supernatant for Western analyses." See, page 2 of the Office Action dated May 1, 2003 (Paper No. 26). The Examiner asserts that "at the point the protein was isolated in the supernatant that had DMEM in it, the claims drawn to a pharmaceutical composition were anticipated." Id.

The Examiner relies on ATCC Catalog No. 30-2002 for the description of DMEM and the assertion that the same is "useful as an in vivo solution, thereby meeting the pharmaceutical composition limitation." Id.

The applicants again urge the Examiner to appreciate that the pending claims call for a pharmaceutically acceptable excipient. DMEM is not a pharmaceutically acceptable excipient and the Examiner is requested to consider the following in this regard.

DMEM includes the following constituents:

- CaC12 (anhydrous);
- Fe(NO3)3-9H2O;

- MgS04 (anhydrous);
- KCl;
- NaCl;
- NaHC03;
- NaH2P04*H20;
- Choline Chloride;
- Folic Acid;
- myo-Inositol;
- Nicotinamide;
- D-Pantothenic Acid (hemicalcium);
- Pyridoxine-HCl;
- Riboflavin;
- Thiamine-HCl;
- L-Arginine-HCl;
- L-Cystine-2HCl;
- L-Glutamine;
- Glycine;
- L-Histidine-HCl-H2O;
- L-Isoleucine;
- L-Leucine;
- L-Lysine.HCl;
- L-Methionine;
- L-Phenylalanine;
- L-Serine;
- L-Threonine;
- L-Tryptophan;
- L-Tyrosine-2Na-2H2O;
- L-Valine;
- D-Glucose;
- Phenol Red, Sodium Salt; and
- Sodium Pyruvate.

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Among the listed constituents of DMEM are the following:

Choline Chloride, Folic Acid, Myo-Inositol, Nicotinamide, D-Pantothenic Acid (hemicalcium), Pyridoxine-HCl,Riboflavin, Thiamine-HCl, L-Arginine-HClL-Cystine-2HCl, L-Glutamine, Glicine, L-Histidine-HCl-H2O, L-Isoleucine, L-Leucine, L-Lysine.HCl, L-Methionine, L-Phenylalanine, L-Serine, L-Threonine, L-Tryptophan, Tyrosine-2Na-2H2O, L-Valine, Sodium Pyruvate.

These components will be recognized by one of ordinary skill in the art to be drug substances such that the inclusion of the same in DMEM would lead one of ordinary

skill in the art to appreciate that DMEM is not a pharmaceutically acceptable excipient, as the term is generally recognized in the art.

The Examiner is requested to see in this regard, for example, the attached copy of page 48 of the Merck Manual which describes the use of Nicotinamide (also known as niacinamide) for treating pellagra. Also attached is copy of page 16611 of the Merck Manual which described the use of folic acid for treating coronary artery disease. The Examiner is also requested to see the attached excerpt from Merck's website which describes choline chloride as having a lipotropic therapeutic activity. Also attached is a printout from the International Program on Chemical Safety indicating that choline chloride is a nutrient and dietary supplement with therapeutic uses. The Examiner is also requested to see the attached printout from the website "suprahealth.com" indicating that folic acid has a number of therapeutic applications. Also attached is a copy of a printout from the website of "biopsychiatry.com" indicating that myo-inositol has therapeutic capacity and applications. Similarly, a printout from Blue Cross also indicates that therapeutic activity of myo-inositol. Further evidence could be provided for the other listed compounds upon the Examiner's further request. The applicants respectfully submit that, in view of the attached, DMEM is not a pharmaceutically acceptable excipient.

Beyond the above and attached, and perhaps more importantly, the supernatant of the cited reference which is referred to by the Examiner and described on page 3485, first full paragraph, of Alles would not be understood by one of ordinary skill in the art to be an administerable pharmaceutical composition, as claimed. More specifically, the solution indicated by the Examiner to allegedly anticipate the presently claimed

invention, would be understood by one of ordinary skill in the art to contain, for example COS cells metabolites, catabolites and residual components of the cellular lysis, such as virus related or released by the DNA of the COS cells. The applicants submit therefore that the PTX3 protein described in the cited art and relied upon by the Examiner is dissolved in a solution which, more likely than not, may be toxic and/or infective such that the solution is not a pharmaceutically acceptable excipient and the composition is not adminsterable as a pharmaceutical composition. Accordingly, the claims are submitted to be patentable over the cited art which fails to teach each and every aspect of the presently claimed invention.

Withdrawal of the Section 102 rejection of claims 17-19 is requested along with a Notice of Allowance.

The undersigned requests an interview with the Examiner, prior to issuance of a further Action, if the claims continue to be rejected for any reason after entry and consideration of the above and the attached.

Respectfully submitted,

NIXON & VANDERHYE P.C.

By: _____
B. J. Sadoff
Reg. No. 36,663

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Facsimile: (703) 816-4100

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Herb Index

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Inositol (Vitamin B8)

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Below:

Introduction

Inositol, unofficially referred to as "vitamin B_8," is present in all animal tissues, with the highest levels in the heart and brain. It is part of the membranes (outer linings) of all cells, and plays a role in helping the liver process fats as well as contributing to the function of muscles and nerves.

Inositol may also be involved in depression. People who are depressed have much lower-than-normal levels of inositol in their spinal fluid. In addition, inositol participates in the action of *serotonin,* a neurotransmitter known to be a factor in depression. (Neurotransmitters are chemicals that transmit messages between nerve cells.) For this reason, inositol has been proposed as a treatment for depression, and preliminary evidence suggests that it may be helpful.

Inositol has also been tried for other psychological and nerve-related conditions.

Sources

Inositol is not known to be an essential nutrient. However, nuts, seeds, beans, whole grains, cantaloupe, and citrus fruits supply a substance called phytic acid (inositol hexaphosphate, or IP6), which releases inositol when acted on by bacteria in the digestive tract. The typical American diet provides an estimated 1,000 mg daily.

Therapeutic Dosages

Experimentally, inositol dosages of up to 18 g daily have been tried for various conditions.

Therapeutic Uses

Some but not all studies suggest that high-dose inositol may be useful for depression.[1-4]

Inositol has also been studied for bipolar disorder,[5] panic disorder,[6,7] bulimia,[8] and obsessive-compulsive disorder,[9,10] but the evidence remains far from conclusive. Other potential uses include Alzheimer's disease[11] and attention deficit disorder.[12]

SITE AWARDS

Inositol is also sometimes proposed as a treatment for complications of diabetes, specifically diabetic neuropathy, but there have been no double-blind placebo-controlled studies, and two uncontrolled studies had mixed results.[13,14]

Inositol has also been investigated for potential cancer-preventive properties.[15-22]

What Is the Scientific Evidence for Inositol?

Depression

Small double-blind studies have found inositol helpful for depression.[23,24]In one such trial, 28 depressed individuals were given a daily dose of 12 g of inositol for 4 weeks.[25] By the fourth week, the group receiving inositol showed significant improvement compared to the placebo group.

A double-blind study of 42 people with severe depression that was not responding to standard antidepressant treatment found no improvement when inositol was added.[26]

Panic Disorder

People with panic disorder frequently develop panic attacks, often with no warning. The racing heartbeat, chest pressure, sweating, and other physical symptoms can be so intense that they are mistaken for a heart attack. A small double-blind study (21 participants) found that people given 12 g of inositol daily had fewer and less severe panic attacks as compared to the placebo group.[27]

A double-blind crossover study of 20 individuals compared inositol to the antidepressant drug fluvoxamine (Luvox), a medication related to Prozac.[28] The results over 4 weeks of treatment showed that the supplement was at least as effective as the drug.

Safety Issues

No serious ill effects have been reported for inositol, even with a therapeutic dosage that equals about 18 times the average dietary intake. However, no long-term safety studies have been performed.

Although inositol has sometimes been recommended for bipolar disorder, there is evidence to suggest inositol may trigger manic episodes in people with this condition.[29] If you have bipolar disorder you should not take inositol unless under a doctor's supervision.

Safety has not been established in young children, women who are pregnant or nursing, and those with severe liver and kidney disease. As with all supplements used in multigram doses, it is important to purchase a reputable product, because a contaminant present even in small percentages could add up to a real problem.

References

1. Levine J, Barak Y, Kofman O, et al. Follow-up and relapse analysis of an inositol study of depression. *Isr J Psychiatry Relat Sci.* 1995;32:14-21.

2. Levine J. Controlled trials of inositol in psychiatry. *Eur Neuropsychopharmacol.* 1997;7:147-155.

3. Benjamin J, Agam G, Levine J, et al. Inositol treatment in psychiatry. *Psychopharmacol Bull.* 1995;31:167-175.

4. Nemets B, Mishory A, Levine J, et al. Inositol addition does not improve depression in SSRI

treatment failures. *J Neural Transm.* 1999;106:795-798.

5. Chengappa KN, Levine J, Gershon S, et al. Inositol as an add-on treatment for bipolar depression. *Bipolar Disord.* 2000;2:47-55.

6. Benjamin J, Levine J, Fux M, et al. Double-blind, placebo-controlled, crossover trial of inositol treatment for panic disorder. *Am J Psychiatry.* 1995;152:1084-1086.

7. Palatnik A, Frolov K, Fux M, et al. Double-blind, controlled, crossover trial of inositol versus fluvoxamine for the treatment of panic disorder. *J Clin Psychopharmacol.* 2001;21:335-339.

8. Gelber D, Levine J, Belmaker RH. Effect of inositol on bulimia nervosa and binge eating. *Int J Eat Disord.* 2001;29:345-348.

9. Fux M, Levine J, Aviv A, et al. Inositol treatment of obsessive-compulsive disorder. *Am J Psychiatry.* 1996;153:1219-1221.

10. Fux M, Benjamin J, Belmaker RH. Inositol versus placebo augmentation of serotonin reuptake inhibitors in the treatment of obsessive-compulsive disorder: a double-blind cross-over study. *Int J Neuropsychopharmcol.* 1999;2:193-195.

11. Levine J. Controlled trials of inositol in psychiatry. *Eur Neuropsychopharmacol.* 1997;7:147-155.

12. Levine J. Controlled trials of inositol in psychiatry. *Eur Neuropsychopharmacol.* 1997;7:147-155.

13. Salway JG, Finnegan JA, Barnett D, et al. Effect of myo-inositol on peripheral-nerve function in diabetes. *Lancet.* 1978;2:1282-1284.

14. Gregersen G, Bertelsen B, Harbo H, et al. Oral supplementation of myoinositol: effects on peripheral nerve function in human diabetics and on the concentration in plasma, erythrocytes, urine and muscle tissue in human diabetics and normals. *Acta Neurol Scand.* 1983;67:164-172.

15. Wattenberg LW. Chemoprevention of pulmonary carcinogenesis by myo-inositol. *Anticancer Res.* 1999;19:3659-3661.

16. Dong Z, Huang C, Ma WY. PI-3 kinase in signal transduction, cell transformation, and as a target for chemoprevention of cancer. *Anticancer Res.* 1999;19:3743-3747.

17. Yang GY, Shamsuddin AM. IP6-induced growth inhibition and differentiation of HT-29 human colon cancer cells: involvement of intracellular inositol phosphates. *Anticancer Res.* 1995;15:2479-2487.

18. Ishikawa T, Nakatsuru Y, Zarkovic M, et al. Inhibition of skin cancer by IP6 in vivo: initiation-promotion model. *Anticancer Res.* 1999;19(5A):3749-3752.

19. Shamsuddin AM. Metabolism and cellular functions of IP6: a review. *Anticancer Res.* 1999;19 (5A):3733-3736.

20. Shamsuddin AM, Vucenik I. Mammary tumor inhibition by IP6: a review. *Anticancer Res.* 1999;19 (5A):3671-3674.

21. Vucenik I, Kalebic T, Tantivejkul K, et al. Novel anticancer function of inositol hexaphosphate: inhibition of human rhabdomyosarcoma in vitro and in vivo. *Anticancer Res.* 1998;18(3A):1377-1384.

22. Shamsuddin AM, Vucenik I, Cole KE. IP6: a novel anti-cancer agent. *Life Sci.* 1997;61:343-354.

23. Levine J, Barak Y, Kofman O, et al. Follow-up and relapse analysis of an inositol study of depression. *Isr J Psychiatry Relat Sci.* 1995;32:14-21.

24. Levine J. Controlled trials of inositol in psychiatry. *Eur Neuropsychopharmacol.* 1997;7:147-155.

25. Benjamin J, Agam G, Levine J, et al. Inositol treatment in psychiatry. *Psychopharmacol Bull.* 1995;31:167-175.

26. Nemets B, Mishory A, Levine J, et al. Inositol addition does not improve depression in SSRI treatment failures. *J Neural Transm.* 1999;106:795-798.

27. Benjamin J, Levine J, Fux M, et al. Double-blind, placebo-controlled, crossover trial of inositol treatment for panic disorder. *Am J Psychiatry.* 1995;152:1084-1086.

28. Palatnik A, Frolov K, Fux M, et al. Double-blind, controlled, crossover trial of inositol versus fluvoxamine for the treatment of panic disorder. *J Clin Psychopharmacol.* 2001;21:335-339.

29. Levine J, Witztum E, Greenberg BD, et al. Inositol-induced mania? [letter]. *Am J Psychiatry.* 1996;153:839.

Reviewed By HealthGate CAM Medical Review Board
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First published May 12, 2000
Last updated March 1, 2002

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Temporal dissociation between lithium-induced changes in frontal lobe myo-inositol and clinical response in manic-depressive illness

by
Moore GJ, Bebchuk JM, Parrish JK, Faulk MW, Arfken CL, Strahl-Bevacqua J, Manji HK
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Am J Psychiatry 1999 Dec; 156(12):1902-8

ABSTRACT

OBJECTIVE: The most widely accepted hypothesis regarding the mechanism underlying lithium's therapeutic efficacy in manic-depressive illness (bipolar affective disorder) is the inositol depletion hypothesis, which posits that lithium produces a lowering of myo-inositol in critical areas of the brain and the effect is therapeutic. Lithium's effects on in vivo brain myo-inositol levels were investigated longitudinally in 12 adult depressed patients with manic-depressive illness. METHOD: Medication washout (minimum 2 weeks) and lithium administration were conducted in a blinded manner. Regional brain myo-inositol levels were measured by means of quantitative proton magnetic resonance spectroscopy at three time points: at baseline and after acute (5-7 days) and chronic (3-4 weeks) lithium administration. RESULTS: Significant decreases (approximately 30%) in myoinositol levels were observed in the right frontal lobe after short-term administration, and these decreases persisted with chronic treatment. The severity of depression measured by the Hamilton Depression Rating Scale also decreased significantly over the study. CONCLUSIONS: This study demonstrates that lithium administration does reduce myo-inositol levels in the right frontal lobe of patients with manic-depressive illness. However, the acute myo-inositol reduction occurs at a time when the patient's clinical state is clearly unchanged. Thus, the short-term reduction of myo-inositol per se is not associated with therapeutic response and does not support the inositol depletion hypothesis as originally posited. The hypothesis that a short-term lowering of myo inositol results in a cascade of secondary signaling and gene expression changes in the CNS that are ultimately associated with lithium's therapeutic efficacy is under investigation.

OCD
SAMe

Cannabis
Kava-kava
Hyperforin
Moodfoods
Herbal highs
Lithium at 50
St John's wort
Inositol depletion
Goldfish on inositol
Inositol and depression
Inositol as an antidepressant
Lithium maintenance: review

Refs
HOME
HedWeb
Future Opioids
BLTC Research
Paradise-Engineering
Utopian Pharmacology
The Hedonistic Imperative
When Is It Best To Take Crack Cocaine?

The Good Drug Guide
The Responsible Parent's Guide
To Healthy Mood Boosters For All The Family

Folic Acid

Folic Acid

(folate, folacin)

FOLIC ACID: Information on folic acid (folate, folacin).

RDA or AI for Adults

- Non-pregnant adults: 400 mcg; During pregnancy: 600 mcg (Prevents some birth defects.)

Adult Maintenance - Therapeutic Range

- 200 - 1,000 mcg. (At high doses, balance with extra vitamin B12.)

Major Sources

- Green leafy vegetables, organ meats (liver), lean beef, wheat, eggs, fish, dry beans, lentils, cowpeas, asparagus, broccoli, collards, yeast. Synthesized by intestinal bacteria.

Non-Therapeutic Importance

- Appears essential for biosynthesis of nucleic acids; essential for normal maturation of red blood cells; functions as the coenzyme, tetrahydrofolic acid.

Deficiency Symptoms

- Confusion
- Depression
- Diarrhea
- Fatigue
- Megaloblastic anemia

Increased Risk for Deficiency

- Alcoholism
- Anorexia
- Anticonvulsant drugs
- Diverticulosis
- Elderly

Hemolytic anemias

- Malabsorption diseases
- Malignancies
- Oral contraceptive agents
- Pregnancy and lactation
- Vitamin B12 deficiency

Possible Therapeutic Applications

CONSULT WITH A HEALTH PROFESSIONAL FIRST: Folic acid works with vitamin B12 in reducing homocysteine, a risk factor for heart disease. Supplementation *may* prevent, correct deficiencies caused by, or be helpful with, the following conditions:

- Acne
- Acquired Immunodeficiency Syndrome (AIDS, HIV)
- Aging
- Alcoholism
- **Atherosclerosis (heart disease)**
- Cancer
- Cardiac Arrhythmias
- Cataracts
- **Celiac Disease**
- **Cerebrovascular Disease (including stroke)**
- Chronic Fatigue Syndrome (CFS, CFIDS)
- Constipation
- **Crohn's Disease**
- Eating Disorders (anorexia, bulimia)
- Gout
- Hypercholesterolemia (high cholesterol)
- Immunodepression (immune function)
- Infection (colds, flu, etc.)
- Infertility (female)
- Infertility (male)
- Intermittent Claudication (poor circulation)
- Irritable Bowel Syndrome (IBS)
- **Memory Loss (Alzheimer's disease, dementia)**
- Multiple Sclerosis (MS)
- **Osteoarthritis**
- Osteoporosis
- Periodontal Disease
- Psoriasis
- Rheumatoid Arthritis
- **Ulcerative Colitis**

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CHOLINE CHLORIDE

0853
October 1995

CAS No: 67-48-1
RTECS No: KH2975000
UN No:
EC No:

(2-Hydroxyethyl)trimethylammonium chloride
Choline hydrochloride
2-Hydroxy-N,N,N-trimethylethanaminium chloride
Cholinium chloride
$C_5H_{14}NO.Cl$
Molecular mass: 139.6

TYPES OF HAZARD/ EXPOSURE	ACUTE HAZARDS/SYMPTOMS	PREVENTION	FIRST AID/FIRE FIGHTING
FIRE	Combustible. Gives off irritating or toxic fumes (or gases) in a fire.	NO open flames.	Water spray, powder.
EXPLOSION			
EXPOSURE			
Inhalation		Ventilation.	Fresh air, rest.
Skin		Protective gloves.	Rinse and then wash skin with water and soap.
Eyes		Safety spectacles.	First rinse with plenty of water for several minutes (remove contact lenses if easily possible), then take to a doctor.
Ingestion		Do not eat, drink, or smoke during work.	

SPILLAGE DISPOSAL	PACKAGING & LABELLING
Sweep spilled substance into containers; if appropriate, moisten first to prevent dusting.	Symbol R: S:

EMERGENCY RESPONSE	STORAGE

IPCS
International Programme on Chemical Safety

Prepared in the context of cooperation between the International Programme on Chemical Safety and the European Commission
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SEE IMPORTANT INFORMATION ON THE BACK.

IMPORTANT DATA

Physical State; Appearance
COLOURLESS TO WHITE HYGROSCOPIC CRYSTALS.

Occupational Exposure Limits
TLV not established. MAK not established.

Routes of Exposure
The substance can be absorbed into the body by ingestion.

Inhalation Risk
No indication can be given about the rate in which a harmful concentration in the air is reached on evaporation of this substance at 20°C.

Effects of Short-term Exposure
See Notes.

Effects of Long-term or Repeated Exposure
Repeated or prolonged contact may cause skin sensitization.

PHYSICAL PROPERTIES

Boiling point (decomposes): 247°C

Solubility in water: miscible

ENVIRONMENTAL DATA

NOTES

The substance is a plant growth inhibitor factor, a nutrient, a dietary supplement and has therapeutic uses. Few data available.

ADDITIONAL INFORMATION

LEGAL NOTICE Neither the EC nor the IPCS nor any person acting on behalf of the EC or the IPCS is responsible for the use which might be made of this information

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THERAPEUTIC CATEGORY AND BIOLOGICAL ACTIVITY INDEX

ABORTIFACIENT/INTERCEPTIVE

Epostane, *3657*
Gemeprost, *4398*
Mifepristone, *6209*
Prostaglandin E_2, *7969*
Prostaglandin $F_{2\alpha}$, *7970*
Sulprostone, *9082*
Trichosanthin, *9721*

ACE-INHIBITOR *see also Antihypertensive*

Alacepril, *200*
Benazepril, *1029*
Captopril, *1780*
Ceronapril, *2005*
Cilazapril, *2295*
Delapril, *2895*
Enalapril, *3599*
Enalaprilat, *3600*
Fosinopril, *4279*
Imidapril, *4934*
Lisinopril, *5538*
Moexipril, *6250*
Moveltipril, *6310*
Omapatrilat, *6912*
Perindopril, *7247*
Quinapril, *8139*
Ramipril, *8194*
Sampatrilat, *8428*
Spirapril, *8827*
Temocapril, *9215*
Trandolapril, *9644*

α-ADRENERGIC AGONIST *see also Antihypotensive; Antihypertensive; Antiulcerative; Decongestant; Mydriatic*

Adrafinil, *170*
Adrenalone, *172*
Amidephrine, *397*
Apraclonidine, *756*
Budralazine, *1456*
Clonidine, *2414*
Cyclopentamine, *2768*
Dexmedetomidine, *2963*
Dimetofrine, *3291*
Dipivefrin, *3372*
Ecabapide, *3521*
Ephedrine, *3639*
Epinephrine, *3650*
Fenoxazoline, *4011*
Guanabenz, *4574*
Guanfacine, *4577*
Hydroxyamphetamine, *4835*
Ibopamine, *4901*
Indanazoline, *4957*
Isometheptene, *5204*
Mephentermine, *5877*
Metaraminol, *5957*
Methoxamine, *6017*
Methylhexaneamine, *6108*
Midodrine, *6208*
Mivazerol, *6241*
Modafinil, *6249*
Moxonidine, *6318*
Naphazoline, *6394*
Norepinephrine, *6727*
Norfenefrine, *6731*
Octodrine, *6789*
Octopamine, *6791*
Oxymetazoline, *7035*
Phenylephrine Hydrochloride, *7370*
Phenylpropanolamine, *7391*
Phenylpropylmethylamine, *7392*
Pholedrine, *7415*
Propylhexedrine, *7952*
Pseudoephedrine, *8007*
Rilmenidine, *8306*
Synephrine, *9104*
Talipexole, *9129*
Tetrahydrozoline, *9292*
Tiamenidine, *9494*
Tramazoline, *9643*
Tuaminoheptane, *9873*
Tymazoline, *9902*
Tyramine, *9903*
Xylometazoline, *10141*

β-ADRENERGIC AGONIST *see also Bronchodilator; Cardiotonic; Tocolytic*

Albuterol, *215*
Bambuterol, *955*
Bitolterol, *1303*
Carbuterol, *1845*
Clenbuterol, *2369*
Clorprenaline, *2434*
Denopamine, *2913*
Dioxethedrine, *3333*
Dopexamine, *3458*
Ephedrine, *3639*
Epinephrine, *3650*
Etafedrine, *3744*
Ethylnorepinephrine, *3866*
Fenoterol, *4008*
Formoterol, *4269*
Hexoprenaline, *4727*
Ibopamine, *4901*
Isoetharine, *5188*
Isoproterenol, *5237*
Mabuterol, *5663*
Metaproterenol, *5956*
Methoxyphenamine, *6027*
Oxyfedrine, *7031*
Pirbuterol, *7572*
Prenalterol, *7824*
Procaterol, *7848*
Protokylol, *7988*
Reproterol, *8224*
Rimiterol, *8311*
Ritodrine, *8320*
Salmeterol, *8416*
Soterenol, *8801*
Terbutaline, *9234*
Tretoquinol, *9662*
Tulobuterol, *9881*
Xamoterol, *10112*

α-ADRENERGIC BLOCKER *see also Antihypertensive*

Amosulalol, *579*
Arotinolol, *797*
Dapiprazole, *2846*
Doxazosin, *3466*
Ergoloid Mesylates, *3685*
Fenspiride, *4027*
Idazoxan, *4912*
Indoramin, *4992*
Labetalol, *5344*
Monatepil, *6268*
Naftopidil, *6382*
Nicergoline, *6521*
Prazosin, *7803*
Tamsulosin, *9138*
Terazosin, *9229*
Tolazoline, *9583*
Trimazosin, *9771*
Yohimbine, *10157*

β-ADRENERGIC BLOCKER *see also Antianginal; Antiarrhythmic; Antiglaucoma; Antihypertensive*

Acebutolol, *19*
Alprenolol, *311*
Amosulalol, *579*
Arotinolol, *797*
Atenolol, *863*
Befunolol, *1023*
Betaxolol, *1186*
Bevantolol, *1194*
Bisoprolol, *1294*
Bopindolol, *1324*
Bucindolol, *1446*
Bucumolol, *1453*
Bufetolol, *1460*
Bufuralol, *1467*
Bunitrolol, *1477*
Bupranolol, *1484*
Butidrine Hydrochloride, *1522*
Butofilolol, *1527*
Carazolol, *1785*
Carteolol, *1881*
Carvedilol, *1888*
Celiprolol, *1972*
Cetamolol, *2027*
Cloranolol, *2428*
Dilevalol, *3224*
Esmolol, *3734*
Indenolol, *4965*
Labetalol, *5344*
Landiolol, *5370*
Levobunolol, *5483*
Mepindolol, *5881*
Metipranolol, *6161*
Metoprolol, *6172*
Moprolol, *6287*
Nadolol, *6372*
Nadoxolol, *6373*
Nebivolol, *6459*
Nifenalol, *6556*
Nipradilol, *6590*
Oxprenolol, *7021*
Penbutolol, *7153*
Pindolol, *7525*
Practolol, *7786*
Pronethalol, *7882*
Propranolol, *7932*
Sotalol, *8800*
Sulfinalol, *9036*
Talinolol, *9128*
Tertatolol, *9250*
Tilisolol, *9515*
Timolol, *9521*
Toliprolol, *9593*
Xibenolol, *10131*

ADRENOCORTICAL STEROID *see Glucocorticoid; Mineralocorticoid*

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LAXATIVE/CATHARTIC (*continued*)

Seidlitz Mixture, *8499*
Senna, *8528*
Sennosides, *8529*
Sodium Phosphate, Dibasic, *8733*
Sodium Succinate, *8754*
Sodium Sulfate, *8755*
Sodium Tartrate, *8759*
Sorbitol, *8797*
Sulisatin, *9073*

LEUKOTRIENE ANTAGONIST *see also* ***Antiasthmatic***

Ibudilast, *4904*
Montelukast, *6281*
Pranlukast, *7795*
Zafirlukast, *10162*

LH-RH AGONIST *see also* ***Antineoplastic; Gonad-Stimulating Principle***

Buserelin, *1491*
Deslorelin, *2940*
Goserelin, *4541*
Histrelin, *4743*
Leuprolide, *5478*
Nafarelin, *6377*
Triptorelin, *9818*

LH-RH ANTAGONIST *see also* ***Antineoplastic***

Cetrorelix, *2036*
Ganirelix, *4380*

LIPOTROPIC

N-Acetylmethionine, *98*
Choline Chloride, *2226*
Choline Dehydrocholate, *2227*
Choline Dihydrogen Citrate, *2228*
Inositol, *5001*
Lecithin, *5447*
Methionine, *6004*

5-LIPOXYGENASE INHIBITOR *see also* ***Antiallergic; Antiasthmatic; Anti-inflammatory; Antipsoriatic***

Amlexanox, *490*
Lonapalene, *5586*
Tenidap, *9221*
Zileuton, *10178*

LOCAL ANESTHETIC *see* ***Anesthetic (Local)***

LUPUS ERYTHEMATOSUS SUPPRESSANT

Bismuth Sodium Triglycollamate, *1281*
Chloroquine, *2182*
Hydroxychloroquine, *4843*

MAJOR TRANQUILIZER *see* ***Antipsychotic***

MATRIX METALLOPROTEINASE INHIBITOR

Batimastat, *1011*
Prinomastat, *7840*

MINERALOCORTICOID

Aldosterone, *224*
Deoxycorticosterone, *2917*
Deoxycorticosterone Acetate, *2918*
Fludrocortisone, *4156*

MINOR TRANQUILIZER *see* ***Anxiolytic***

MIOTIC

Carbachol, *1786*
Neostigmine, *6492*
Physostigmine, *7469*
Pilocarpine, *7505*

MONOAMINE OXIDASE INHIBITOR *see also* ***Antidepressant; Antihypertensive; Antiparkinsonian***

Befloxatone, *1022*
Iproclozide, *5095*
Iproniazid, *5097*
Isocarboxazid, *5174*
Lazabemide, *5411*
Moclobemide, *6247*
Mofegiline, *6253*
Octamoxin, *6781*
Pargyline, *7110*
Phenelzine, *7300*
Phenoxypropazine, *7342*
Pivalylbenzhydrazine, *7595*
Prodipine, *7857*
Selegiline, *8502*
Toloxatone, *9599*
Tranylcypromine, *9649*

MUCOLYTIC

Acetylcysteine, *90*
Bromhexine, *1375*
Carbocysteine, *1812*
Domiodol, *3448*
Erdosteine, *3677*
Letosteine, *5468*
Lysozyme, *5660*
Mecysteine Hydrochloride, *5809*
Mesna, *5936*
Sobrerol, *8638*
Stepronin, *8887*
Tiopronin, *9532*
Tyloxapol, *9901*

MUSCLE RELAXANT (SKELETAL) *see also* ***Neuromuscular Blocking Agent***

Afloqualone, *183*
Baclofen, *939*
Botulin Toxins, *1345*
Carisoprodol, *1854*
Chlormezanone, *2122*
Chlorphenesin Carbamate, *2197*
Chlorzoxazone, *2214*
Cyclobenzaprine, *2742*
Dantrolene, *2842*
Diazepam, *3018*
Eperisone, *3637*
Idrocilamide, *4917*
Inaperisone, *4952*
Mephenesin, *5875*
Mephenoxalone, *5876*
Methocarbamol, *6010*
Mivacurium Chloride, *6240*
Orphenadrine, *6945*
Phenprobamate, *7343*
Pridinol Mesylate *see 7830*
Quinine, *8151*
Tetrazepam, *9315*
Thiocolchicoside *see 9398*
Tizanidine, *9561*
Tolperisone, *9600*

MUSCLE RELAXANT (SMOOTH) *see* ***Antimuscarinic***

MYDRIATIC

Atropine, *879*
Cyclodrine, *2748*
Cyclopentolate, *2775*
Epinephrine, *3650*
Eucatropine, *3930*
Homatropine, *4750*
Hydroxyamphetamine, *4835*
Phenylephrine Hydrochloride, *7370*
Scopolamine, *8481*
Tropicamide, *9850*
Yohimbine, *10157*

NARCOTIC ANALGESIC *see* ***Analgesic (Narcotic)***

NARCOTIC ANTAGONIST

Amiphenazole, *483*
Cyclazocine, *2733*
Levallorphan, *5479*
Nalmefene, *6386*
Nalorphine, *6387*
Naloxone, *6388*
Naltrexone, *6389*

NASAL DECONGESTANT *see* ***Decongestant***

NEURAMINIDASE INHIBITOR *see also* ***Antiviral***

Oseltamivir, *6958*
Zanamivir, *10167*

NEUROLEPTIC *see* ***Antipsychotic***

NEUROMUSCULAR BLOCKING AGENT

Depolarizing Agents

Decamethonium Bromide, *2867*
Succinylcholine Bromide, *8958*
Succinylcholine Chloride, *8959*
Succinylcholine Iodide, *8960*

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Pellagra

pigmented over pressure points, secondary infection often develops, and the lesion has a sharply defined pearly border of regenerating epithelium when healing begins
- Chronic atrophic lesions, with dry, scaly, melastic skin too large for the part it covers (seen in older pellagrins).

The distribution of lesions—at trauma points—is more characteristic than their form. Sunlight causes Casal's necklace and butterfly-shaped lesions on the face.

Mucous membrane symptoms primarily affect the mouth but may also affect the vagina and urethra. Scarlet glossitis and stomatitis are characteristic of acute deficiency. The tip and margins of the tongue and the mucosa around Stensen's duct are affected first. As the lesion progresses, the entire tongue and oral mucous membranes become bright scarlet, followed by a sore mouth, increased salivation, and edema of the tongue. Ulcerations may appear, especially under the tongue, on the mucosa of the lower lip, and opposite the molar teeth. They are often covered by a grayish slough containing Vincent's organisms.

GI symptoms, which are indeterminate in early cases, include burning of the mouth, pharynx, and esophagus and abdominal discomfort and distention. Later, nausea, vomiting, and diarrhea may occur. Diarrhea, often bloody because of GI hyperemia and ulceration, is serious.

CNS symptoms include organic psychosis, characterized by memory impairment, disorientation, confusion, and confabulation (excitement, depression, mania, and delirium predominate in some patients; in others, the reaction is paranoid); and (2) encephalopathic syndrome, characterized by clouding of consciousness, cogwheel rigidity of the extremities, and uncontrollable sucking and grasping reflexes. Differentiating these CNS changes from those in thiamine deficiency is difficult.

Diagnosis and Treatment

Niacin deficiency must be distinguished from other causes of stomatitis, glossitis, diarrhea, and dementia. Diagnosis is easy when the clinical findings include skin and mouth lesions, diarrhea, delirium, and dementia. More often, the condition is less fully developed, and a history of a diet lacking niacin and tryptophan is significant. Urinary excretion of N'-methylnicotinamide (NMN) and its pyridone is decreased. NMN excretion of < 0.8 mg/day suggests a niacin deficiency.

Multiple deficiencies of B vitamins and protein often occur together, therefore, a balanced diet is needed. Supplemental niacinamide 300 to 1000 mg/day should be given orally in divided doses. In most cases, 300 to 500 mg is sufficient. Niacinamide is generally used to treat deficiency states, because niacin can cause flushing, itching, burning, or tingling sensations, whereas niacinamide does not; however, niacinamide does not possess hypolipidemic or vasodilating properties as does niacin. When oral therapy is precluded because of diarrhea or lack of patient cooperation, 100 to 250 mg should be injected sc bid to tid. In encephalopathic states, 1000 mg po plus 100 to 250 mg IM is recommended. Other B-complex vitamins should also be given in therapeutic dosages.

VITAMIN B_6 DEFICIENCY AND DEPENDENCY

Vitamin B_6 comprises a group of closely related compounds: pyridoxine, pyridoxal, and pyridoxamine. They are metabolized and phosphorylated in the body to pyridoxal phosphate, which functions as a coenzyme in many reactions, including decarboxylation and transamination of amino acids, deamination of hydroxyamino acids and cysteine, conversion of tryptophan to niacin, and metabolism of fatty acids. Consequently, the vitamin B_6 group is important in blood, CNS, and skin metabolism. Vitamin B_6 is important in erythropoiesis because pyridoxal phosphate is needed in the formation of δ-aminolevulinic acid, the rate-limiting step in heme biosynthesis.

Primary deficiency is rare, because most foods contain vitamin B_6. Nonetheless, an outbreak of convulsions in infants did follow the inadvertent destruction of vitamin B_6 in infant formulas. Secondary deficiency may result from malabsorption, alcoholism, oral contraceptive use, chemical inactivation by drugs (eg, isonicotinic acid hydrazide, cycloserine, hydralazine, penicillamine), excessive loss, and increased metabolic activity.

Symptoms and Signs

Deficiency: The vitamin B_6 antagonist deoxypyridoxine produces seborrheic dermatosis, glossitis, cheilosis, peripheral neuropathy, and lymphopenia. Vitamin B_6 deficiency can cause convulsions in infants and anemia in adults (usually normocytic but occasionally microcytic).

Dependency: Several recessive or X-linked states affect different vitamin B_6 apoenzymes, producing symptoms such as convulsions, mental deficiency, cystathionuria, sideroblastic (iron overload) anemia, urticaria, asthma, and xanthurenic aciduria.

Laboratory Findings and Diagnosis

At present, there is no generally accepted test of vitamin B_6 status. The whole blood level of pyridoxal phosphate is a better indicator than the plasma level. Erythrocyte glutamic pyruvate and oxaloacetic transaminase activities are decreased in vitamin B_6 deficiency, but these changes are not diagnostic because of the wide range of values in healthy persons.

Treatment

Underlying causes such as use of pyridoxine-inactivating drugs (anticonvulsants, corticosteroids, estrogens, isoniazid, penicillamine, and hydralazine) or malabsorption should be corrected. For dependency in infants, the daily requirement (normally 0.4 mg) is increased many times (up to 10 mg). For pyridoxine-dependent seizures, the initial dose is 50 to 100 mg IM or IV daily for 1 wk followed by oral doses tapered over 1 wk to 25 mg. Deficiency in adults usually responds to pyridoxine 50 to 100 mg/day po. Conditions that increase metabolic demand, such as hyperthyroidism and diabetes, require amounts in excess of the recommended allowance. For pyridoxine deficiency associated with drugs such as isoniazid, 100 mg/day may be required. For dependency in adults, as much as 200 to 600 mg daily of pyridoxine may be needed.

VITAMIN B_6 TOXICITY

The ingestion of megadoses (2 to 6 g/day for 2 to 40 mo) of pyridoxine, mistakenly taken for premenstrual tension, may cause progressive sensory ataxia and profound lower limb impairment of position and vibration sense. Senses of touch, temperature, and pain are less affected. The motor and central nervous systems are unimpaired. Recovery is slow and, in some patients, is only partial after pyridoxine ingestion is stopped.

BIOTIN DEFICIENCY AND DEPENDENCY

Biotin functions as a coenzyme for carbon dioxide transfer and hence is essential to fat and carbohydrate metabolism. A specific enzyme links biotin to its apoenzymes.

Deficiency: Raw egg white contains a biotin antagonist, avidin. Prolonged consumption of raw egg whites may result in dermatitis and glossitis, which respond rapidly to 150 to 300 μg biotin daily. Deficiency has also occurred during long-term TPN without supplementary biotin.

Dependency: Retarded physical and mental development, alopecia, keratoconjunctivitis, and defects in T-cell and B-cell immunity have been reported in children with deficiencies of multiple biotin-dependent carboxylases. Deficiencies result from mutations in holocarboxylase synthetase (the enzyme required to link biotin to four carboxylases necessary for metabolism) or in biotinidase (the enzyme required to remove biotin from the same enzymes in catabolism). Urinary excretion of various organic acids assists diagnosis. Children with holocarboxylase synthetase and biotinidase abnormalities respond well to large doses of biotin (5 to 20 mg) daily.

PANTOTHENIC ACID DEFICIENCY

Pantothenic acid is a vitamin widely distributed in foodstuffs and is an essential component of coenzyme A, which functions as an acyltransfer cofactor for many enzymatic reactions. Adults probably require about 4 to 7 mg/day, corresponding to a whole blood level of 100 to 180 μg/dL (4.56 to 8.21 μmol/L), but no RDA has been set. Pantothenic acid deficiency is rarely observed in humans.

Adult volunteers on a deficient diet experienced malaise, abdominal discomfort, and burning feet associated with paresthesias, which responded to pantothenic acid. In

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TABLE 202–1. TYPES OF DIETARY FAT

Fats	Sources
Saturated fats	Meats, non-skim dairy products, artificially hydrogenated vegetable oils
Monounsaturated fats	Olive oil, canola oil
Polyunsaturated fats	
Omega-3 oils	Sea plankton, deep-sea cold-water fatty fish (eg, tuna, salmon, mackerel)
Omega-6 oils	Cultivated vegetable oils (eg, corn oil)

Association recommends that the proportion be reduced to 30%, yet a reduction to < 10% may be needed to have a major effect on CAD risk.

The type of dietary fat is also important; there are three kinds (TABLE 202–1): saturated, monounsaturated, and omega-3 and omega-6 PUFAs. The ideal proportion of each of these fats is unknown. However, diets high in saturated fats are clearly atherogenic, and those high in monounsaturates or omega-3 oils are less so.

U.S. studies failed to show a decreased incidence of angina or MI in persons eating diets high in omega-3 oils, although such diets were associated with decreased risk of sudden cardiac death. Persons eating the most fish consumed an average of 0.58 g/day of omega-3 oils, but much higher intakes of omega-3 oils are probably needed for demonstrable risk factor reduction. For example, omega-3 oil supplementation with two or three divided doses of eicosapentaenoic acid 1.8 to 6 g/day and docosahexaenoic acid 0.75 to 2.5 g/day lowers elevated serum triglyceride levels. These doses are up to 10 times the amounts consumed by the fish eaters in the U.S. studies.

For patients at high risk of CAD and especially for those with evidence of CAD, it is reasonable to recommend a 20 g/day fat diet consisting of 6 to 10 g of PUFAs with equal proportions of omega-6 and omega-3 oils, ≤ 2 g of saturated fat, and the remainder as monounsaturates.

Fruits and vegetables: Five servings/day of fruits and vegetables, which are rich in phytochemicals, seems to decrease the risk of CAD and some cancers. However, populations eating a high phytochemical diet also tend to consume less saturated fat, more fiber, and more vitamin C and E, making the role of phytochemicals less clear. One group of phytochemicals called flavonoids (found in red and purple grapes, red wine, black teas, and dark beers) appear particularly protective against CAD. High intake of flavonoids in red wine may help explain why French populations have a relatively low incidence of CAD, despite using more tobacco and consuming more fat than Americans do.

Fiber: Americans eat relatively little fiber, of which there are two kinds: soluble fiber (found in oat bran and psyllium), which decreases total cholesterol and may have a beneficial effect on glucose and insulin levels, and insoluble fiber (eg, cellulose, lignin). Fiber is not without adverse effects, however, such as interfering with the absorption of certain minerals and vitamins. In general, foods rich in phytochemicals and vitamins are also rich in fiber.

Vegetable proteins: Consumption of vegetable proteins (eg, soy, tempeh, seitan) seems to decrease CAD risk.

DIETARY SUPPLEMENTATION

Dietary supplementation with vitamins, phytochemicals, omega-3 oils, and trace minerals remains controversial. There are data to justify supplementation with vitamin E, vitamin C, folic acid, and Ca but less convincing data to support the use of vitamin B_6 and B_{12}.

Vitamin E decreases the oxidation of serum LDL-C and thus appears to reduce its capability for vascular damage. Serum vitamin E levels are inversely correlated with incidence of cardiovascular mortality, and supplementation with vitamin E 800 IU/day has been shown to decrease the incidence of MI. A recent study among nurses showed that diets higher in vitamin E were associated with lower death rates from heart disease but failed to show a specific benefit of vitamin E supplementation, possibly because of problems with study design and data collection. Further studies are underway.

Although it has not been shown to decrease the risk of heart disease, supplementation with vitamin C 250 to 500 mg bid increases the antioxidant properties of vitamin E.

Folic acid 0.8 mg bid prevents CAD by lowering elevated levels of homocysteine. Vitamins B_6 and B_{12} also lower homocysteine levels, but evidence justifying their use in general prevention is scanty. Calcium 500 mg bid, aside from its other benefits, appears to have a role in normalizing BP in certain persons.

EXERCISE

Recent studies have shown that increased levels of physical activity and fitness are associated with a decreased incidence of heart disease and hypertension. However, there have been no controlled trials on the optimal intensity, duration, frequency, or type of exercise. Also, the question of whether people with healthy hearts choose more active lifestyles or whether active lifestyles lead to healthier hearts remains unanswered. Several controlled but small studies demonstrated beneficial effects of exercise on BP and on CAD risk.

Comprehensive cardiac rehabilitation, of which exercise is an important part, decreases long-term morbidity and mortality after MI. It is equally beneficial in patients with angina and in those who have undergone bypass surgery or angioplasty. Cardiac rehabilitation involves the same principles used in the primary prevention of CAD. However, most patients and physicians pay little attention to aggressive prevention of heart disease until signs of CAD appear.

Pre-exercise evaluation should consist of a history and physical examination to exclude such conditions as valvular heart disease, ventricular hypertrophy, dangerous arrhythmias, hypertension, exercise-induced asthma, hemoglobinopathies, and musculoskeletal disease. In adolescents or young adults without abnormal findings, no further workup is generally needed. Evaluation is more extensive in older persons and those who are sick or at increased risk of disease (including those with poorly controlled diabetes, heart disease, hypertension, or obesity). Ideally, such people should have an exercise stress test (see Ch. 198). Further evaluation (eg, by a physical therapist for patients with musculoskeletal problems) should be considered before the start of resistive strength training. Patients with elevated cholesterol levels should have lipoprotein analysis, body fat estimation, and dietary evaluation. Obese patients should have dietary analysis, thyroid function tests, and determinations of blood glucose, insulin levels (both fasting and following oral glucose) and resting metabolic rates may be evaluated in research studies.

There are three kinds of **exercise programs:** those that promote endurance, muscle strength, and flexibility. Endurance and muscle strength have a clear role in CAD prevention. Any complete exercise program should include all three kinds. The American College of Sports Medicine has established minimum exercise recommendations for healthy men and women of all ages to develop and maintain cardiorespiratory fitness, healthy body composition, and muscular strength and endurance (see TABLE 202–2).

Components of endurance exercise include duration, frequency, type, and intensity. Endurance training should last ≥ 40 min/day at least three times/wk. Each ses-

TABLE 202–2. AMERICAN COLLEGE OF SPORTS MEDICINE MINIMUM EXERCISE RECOMMENDATION

Parameter	Recommendation
Frequency	3–5 days/wk
Intensity	To 60–90% of maximum heart rate or to a heart rate at 50–85% of maximum O_2 uptake or heart rate reserve
Duration	20–60 min of continuous aerobic activity depending on intensity
Method	Should use large muscle groups, can be maintained continuously, and is rhythmical and aerobic (eg, walking/hiking, running/jogging, cycling, cross-country skiing, dancing, skipping rope, rowing, stair climbing, swimming, skating)
Resistive strength training	At least one set of 8–12 repetitions of 8–10 exercises that condition the major muscle groups at least twice/wk

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INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

STABILITY TESTING OF NEW DRUG SUBSTANCES AND PRODUCTS Q1A(R2)

Recommended for Adoption
at Step 4 of the ICH Process
on 6 February 2003
by the ICH Steering Committee

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

Excipient
Anything other than the drug substance in the dosage f rm.

Expiration date
The date placed on the container label of a drug product designating the time prior t which a batch of the product is expected to remain within the approved shelf life specification if stored under defined conditions, and after which it must not be used.

Formal stability studies
Long term and accelerated (and intermediate) studies undertaken on primary and/or commitment batches according to a prescribed stability protocol to establish or confirm the re-test period of a drug substance or the shelf life of a drug product.

Impermeable containers
Containers that provide a permanent barrier to the passage of gases or solvents, e.g., sealed aluminum tubes for semi-solids, sealed glass ampoules for solutions.

Intermediate testing
Studies conducted at 30°C/65% RH and designed to moderately increase the rate of chemical degradation or physical changes for a drug substance or drug product intended to be stored long term at 25°C.

Long term testing
Stability studies under the recommended storage condition for the re-test period or shelf life proposed (or approved) for labeling.

Mass balance
The process of adding together the assay value and levels of degradation products to see how closely these add up to 100% of the initial value, with due consideration of the margin of analytical error.

Matrixing
The design of a stability schedule such that a selected subset of the total number of possible samples for all factor combinations is tested at a specified time point. At a subsequent time point, another subset of samples for all factor combinations is tested. The design assumes that the stability of each subset of samples tested represents the stability of all samples at a given time point. The differences in the samples for the same drug product should be identified as, for example, covering different batches, different strengths, different sizes of the same container closure system, and, possibly in some cases, different container closure systems.

Mean kinetic temperature
A single derived temperature that, if maintained over a defined period of time, affords the same thermal challenge to a drug substance or drug product as would be experienced over a range of both higher and lower temperatures for an equivalent defined period. The mean kinetic temperature is higher than the arithmetic mean temperature and takes into account the Arrhenius equation.

When establishing the mean kinetic temperature for a defined period, the formula of J. D. Haynes (*J. Pharm. Sci.*, 60:927-929, 1971) can be used.

New molecular entity
An active pharmaceutical substance not previously contained in any drug product registered with the national or regional authority concerned. A new salt, ester, or non-covalent-bond derivative of

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Butterworths Medical Dictionary

Second Edition

Editor-in-Chief
Macdonald Critchley

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Ewing's sign. Tenderness of the medial part of the floor of the frontal air sinus elicited by digital compression, and suggestive of sinus infection.

ex-. 1. Prefix, from the Latin *ex*, meaning *from, out of, without*. 2. Prefix, from the Greek *ex*, meaning *out*.

exacerbation (ex·as·er·ba'·shun). Increase in severity of a disease or in violence of symptoms. [L *exacerbare* to irritate intensely.]

exaemia (ex·e·me·ah). A condition in which a considerable quantity of blood is temporarily removed from the general circulation, as in shock when blood accumulates in the abdomen, or when a limb is ligatured. [Gk *ex*, *haima* blood.]

exaltation (ex·awl·ta·shun). 1. Abnormal intensification of organic or functional power. 2. Abnormal increase in mental activity. 3. In psychological medicine, exaggerated sense of personal well-being and power, with spiritual ecstasy and delusions of grandeur. [L *exaltare* to raise high.]

examination (ex·am·in·a'·shun). Critical investigation and inspection for diagnostic purposes.

exangeia, exangia (ex·an·je·ah). A state of dilatation of a blood vessel. [Gk *ex*, *aggeion* vessel.]

exanimation (ex·an·im·a'·shun). 1. A state of unconsciousness or coma. 2. A state of fainting. 3. Death. [L *ex*, *animus* soul.]

exanthem (ex·an·them). The rash or eruption produced by the action of an organism or its toxins on the small blood vessels of the skin. **Boston exanthem.** A febrile illness with a macular exanthem and, sometimes, an oral enanthema, caused by *Echovirus 16*. [Gk *ex*, *anthema* blossoming.]

exanthema (ex·an·the·mah) (pl. *exanthemata*). One of a group of infectious diseases in which a specific rash is an important clinical feature and may assist diagnosis. **Exanthema subitum.** Pseudorubella: an eruptive disease resembling rubella in its rash, the enlargement of glands of the neck, and fever, but differing from it in its age incidence, which is exclusively from 6 months to 2 years. The rash fades in 2 or 3 days, and there are no sequelae. Leucopenia with marked relative lymphocytosis may help in diagnosis. [see prec.]

exanthematous (ex·an·them·at·us). 1. Belonging or relating to or having the characteristics of an exanthem. 2. Showing the character of an eruptive disease.

exanthesis (ex·an·the·sis). Any eruption of the skin; an exanthem. **Exanthesis rosalia arthrodynia.** Dengue. [Gk a blossoming.]

exanthrope (ex·an·thrope). Any source outside the human body that gives rise to disease. [Gk *ex*, *anthropos* man.]

exanthropia (ex·an·thro·pe·ah). Morbid aversion to and avoidance of human society. [see prec.]

exanthropic (ex·an·throp·ik). 1. Referring to an exanthrope or exanthropia. 2. Originating outside of or not existing within the human body.

exarteritis (ex·ar·ter·i'·tis). A condition of inflammation of the tunica adventitia of an artery. [Gk *ex*, artery, Gk *-itis* inflammation.]

exarthrima (ex·ar·thrim·ah). Dislocation of a joint. [Gk *ex*, *arthron* joint.]

exarticulation (ex·ar·tik·ew·la'·shun). 1. Dislocation. 2. Amputation of a limb through a joint. 3. Excision of a part of a joint. [L *ex*, *articulatio* joint.]

excalation (ex·kal·a·shun). The exclusion or suppresion of one or more parts or members of a series, as a digit or a vertebra. [L *ex*, *calare* to call.]

excavation (ex·kav·a·shun). The process of scooping out. **Dental excavation.** The process of removing caries from a cavity in a tooth by means of an excavator. **Excavation of the optic disc.** Pallor and hollowing-out of the nerve head; also called *cupping*. It may be *physiological*, confined to the centre of the disc; *glaucomatous*, extending to the edge of the disc and often deep with overhanging edges; *postatrophic*, shallow and saucer-like; or *cavernous*, very deep and thought to be arteriosclerotic in nature, as it is not associated with raised tension. **Excavation of the disc of the optic nerve [excavatio disci (NA)].** The depression at the entry of the optic nerve into the retina; sometimes also termed the *physiological cup*. [L *ex*, *cavus* hollow.]

See also: SCHNABEL.

excavator (ex·kav·a·tor). 1. A large sharp spoon or scoop used to clear a cavity of morbid tissue. 2. In dentistry, an instrument used to clear out a tooth cavity preparatory to the insertion of a filling. **Spoon excavator.** A spoon-shaped dental excavator. [see prec.]

excentric (ek·sen·trik). 1. Eccentric. 2. Away from the centre or the median line. 3. Efferent. [L *ex*, centre.]

excerebration (ek·ser·e·bra'·shun). 1. In obstetrics, removal of the fetal brain in the operation of embryotomy. 2. Removal of the brain in dissection. [L *ex*, cerebrum.]

excess (ek·ses). Departure from normal. **Base excess.** Base concentration per litre of blood measured by acid titration to pH 7.4. **Convergence excess.** A form of muscle imbalance in which there is a tendency to converge, which is more marked for near vision than for distance. [L *excedere* to go out.]

exchange (ex·cha·nj). In cytogenetics, denoting chromosome mutations due to exchange of segments between chromatids of the same chromosome (*intrachange*) or between different chromosomes (*interchange*). [L *ex-*, *cambire* to change.]

excipient (ek·sip·e·ent). A binding agent enabling powdered drugs to be made into pills. Among the liquid excipients are syrup of glucose, mucilage of acacia and simple sugar; among the solids are gum acacia, liquorice, powdered soap and a mixture of gum acacia and tragacanth. Excipients must not have therapeutic action of their own, nor should they be of such a nature as to render the resultant pill insoluble. Colour must also be taken into account, and a white excipient used with white ingredients of a pill. [L *excipere* to take up.]

excise (ek·size). 1. To hollow out. 2. To amputate. 3. To cut away as diseased matter from healthy matter. [L *ex*, *caedere* to cut.]

excision (ek·sizh·un). The act or operation of excising or amputating a part. **Excision of a wound, Wound excision.** Débridement. [see prec.]

See also: LOCKHART-MUMMERY.

excitability (ek·si·tab·il'·it·e). 1. Irritability. 2. A property of living organisms causing them to respond quickly to the action of stimulants or a stimulus. [L *excitare* to rouse.]

excitable (ek·si·tabl). 1. Responding rapidly to stimulus. 2. Capable of being stimulated or excited. [see prec.]

excitant (ek·si·tant). 1. Tending to stimulate. 2. Any agent that stimulates or augments organic activity. 3. Any agent or remedy that stimulates mental function or the vital functions. [see foll.]

excitation (ek·si·ta·shun). 1. A state of being mentally or nervously excited. 2. The condition of being stimulated. 3. The act of increasing the rapidity or the intensity of a process. 4. In physics, the addition of energy to a system, transforming it from its ground state to an excited state. **Anomalous atrioventricular excitation.** Pre-excitation. Wolff-Parkinson-White syndrome. **Direct excitation.** Muscular stimulation brought about by placing an electrode on the muscle itself. **Indirect excitation.** The act of stimulating a muscle by stimulating its nerve. [L *excitare* to rouse.]

excitatory (ek·si·ta·tor·e). 1. Tending or serving to excite or stimulate. 2. Tending to induce disassimilation. [see prec.]

excitement (ek·site·ment). The second stage of anaesthesia. [L *excitare* to rouse.]

excito-anabolic (ek·si·to·an·ab·ol'·ik). Stimulating the process of anabolism. [excitation, anabolism.]

excitocatabolic (ek·si·to·kat·ab·ol'·ik). Stimulating the process of catabolism. [excitation, catabolism.]

excitoglandular (ek·si·to·glan'·dew·lar). Stimulating activity of a gland. [excitation, gland.]

excitometabolic (ek·si·to·met·ab·ol'·ik). Stimulating the activity of the metabolic process; giving rise to changes in metabolism. [excitation, metabolism.]

excit motor, excitomotory (ek·si·to·mo'·tor, ek·si·to·mo'·tor·e). 1. Producing or increasing rapidity of movement. 2. Promoting motor function. 3. Any agent, e.g. a drug, that excites or induces functional or nervous activity or movement. [excitation, motor.]

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Definition of Frequently Used Terms in Regulatory Affairs and Quality Assurance

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Abstract. *The following is a list of terms frequently used in Regulatory Affairs and Quality Assurance, along with their definitions.*

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- **Acceptance Criteria** – Numerical limits, ranges, or other suitable measures for acceptance of the results of analytical procedures.

- **Accuracy** – The "closeness" of the test results obtained by an analytical method to the true value.

- **Active Pharmaceutical Ingredient** – See "Drug Substance."

- **Animal Pharmacology/Toxicology Studies** – Preclinical data to permit an assessment as to whether the product is reasonably safe for initial testing in humans.

- **Batch** – A specific quantity of an intermediate or drug substance intended to have uniform character and quality, within specified limits, and produced according to a single manufacturing order during the same cycle of manufacture. A batch may also mean a specific quantity of material or drug substance processed in one process or series of processes so that it could be expected to be homogenous.

- **Calibration** – The set of operations that establish, under specified conditions, the relationship between values indicated by a measuring instrument or measuring system and the corresponding known values of the measurement.

- **Clinical Investigator Information** – Information on the qualifications of clinical investigators/professionals (generally physicians) who oversee the administration of the experimental compound to assess whether they are qualified to fulfill their clinical trial duties.

- **Clinical Protocols** – Detailed protocols for proposed clinical studies to assess whether the initial phase trials will expose subjects to unnecessary risks.

- **Combination Product** – A drug product that contains more than one drug substance.

- **Compliance Verification Report (CVR)** – A report issued by the Product Information Management Branch of the FDA to all firms that have at least one prescription product listed with the FDA in order to assist with drug product listing requirements.

- **Concurrent Validation** – A subset of prospective validation in which API batches are released for distribution, based on extensive testing, before completion of process validation. Once data from additional batches produced under replicated conditions show uniformity, the process may be considered validated.

- **Controlled Substance** – A drug or other substance, or immediate precursor, included in Schedule I, II, III, IV, or V of Part B of 21 USCS Section 812 (United States Code Service). This term does not include distilled spirits, wine, malt beverages, or tobacco.

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- **Counterfeit Substance** – A controlled substance which, or the container or labeling of which, without authorization, bears the trademark, trade name, or other identifying mark, imprint, number, or device, or any likeness thereof, of a manufacturer, distributor, or dispenser other than the person or persons who in fact manufactured, distributed, or dispensed such substance and which thereby falsely purports or is represented to be the product of, or to have been distributed by, such other manufacturer, distributor, or dispenser.

- **Debarment** – The act of excluding an individual that has been convicted of a crime under federal law for conduct relating to the development or approval of any drug product or otherwise relating to the regulation of any drug product under the Federal Food, Drug, and Cosmetic Act, from providing services in any capacity for the submission, or assisting in the submission, of any approved or pending drug product application.

- **Degradation Product** – A molecule resulting from a chemical change in the drug molecule brought about over time and/or by the action of light, temperature, pH, water, or by reaction with an excipient and/or the immediate container/closure system. Also called *Decomposition Product.*

- **Design Qualification (DQ)** – Defines the functional and operational (or performance) specifications for any piece of equipment and any ancillary systems.

- **Drug** – As defined in Section 201 (g)(1) of the Food, Drug, and Cosmetic Act means (a) articles that are recognized in the official United States Pharmacopoeia, official Homeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to them; (b) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in humans or other animals; and articles (other than food) intended to affect the structure or any function of the body of humans or other animals.

- **Drug Product** – A finished dosage form (e.g. tablet, capsule, or solution) that contains a drug substance generally, but not necessarily, in association with one or more other ingredients. Includes human drugs, veterinary drugs, and medical animal feed premixes which includes biological products, but does not include blood and blood components.

- **Drug Substance** – An active ingredient that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or any function of the body, but does not include intermediates used in the synthesis of such ingredient.

- **Excipient (ICH Q1A)** – Anything other than the drug substance in the dosage form.

- **Expiry/Expiration Date (ICH Q1A)** – The date placed on the container/labels of a drug product designating the time during which a batch of the product is expected to remain within the approved shelf-life specification if stored under defined conditions, and after which it must not be used.

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- **Extractables/Leachables** – Materials or components derived from the container/closure which have been transferred into the contained drug substance of drug product.

- **FDA 482** – A written, signed Notice of Inspection issued to a firm by an FDA Investigator who has the authority to enter and inspect a firm operating at a business location. A FDA 483 may be issued as a result of the inspection.

- **FDA 483** – A listing of observations of objectionable conditions and practices, pursuant to Section 704(b) of the Federal Food, Drug, and Cosmetic Act, to assist firms in complying with the Acts and regulations enforced by the Food and Drug Administration. This listing is presented to the highest management official available upon completing an inspection and before leaving the premises.

- **Final Intermediate** – The last compound synthesized before the reaction that produces the drug substance. The final step forming the new drug substance must involve covalent bond formation; ionic bond formation (i.e. making the salt of a compound) does not qualify. Consequently, when the drug substance is a salt, the precursors to the organic acid or base, rather than the acid or base itself, should be considered the final intermediate.

- **Final Solution Step** – The solution from which the drug substance is isolated in pure form by either crystallization or precipitation. Where the purification procedure for the crude drug substance involves several crystallization or precipitation steps, final solution step refers only to the last of these steps.

- **Firm** – A company engaged in the manufacture, preparation, propagation, compounding, or processing of a drug product.

- **Historical Data** – Data on impurities or physical attributes from ten recent batches representative of the established process. The upper statistical limit of an impurity is generally based on the mean plus three times the standard deviation. [The appropriate review division(s) should be contacted for concurrence in those rare instances (e.g., low-volume drug substances) where evaluation of historical data is based on <10 batches.]

- **Identified Impurity** – An impurity for which a structural characterization has been achieved.

- **Impurity** – Any component of the drug substance that is not the entity defined as the drug substance (ICH Q3A).

- **Impurity Profile** – A description of the identified and unidentified impurities present in a drug substance (ICH Q3A).

- **In Situ Intermediate** – An intermediate that is not isolated. It is normally, but not necessarily, in solution (*Guideline for Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances*).

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- **Installation Qualification (IQ)** – The documented verification that all key aspects of the equipment and ancillary systems installations adhere to the approved design intentions (plans) and that the recommendations of the manufacturer are suitably considered.

- **Instrument Testing** – The process of executing experiments to measure the performance characteristics following documented procedures.

- **Intermediate** – A material produced during steps in the synthesis of an active pharmaceutical ingredient that must undergo further molecular change or processing before it becomes an active pharmaceutical ingredient.

- **International Conference on Harmonization (ICH)** – A project combining the regulatory authorities of Europe, Japan, and the United States, as well as experts in the Pharmaceutical Industry in these three regions, to discuss scientific and technical aspects of product registration. The purpose of the ICH is achieving greater harmonization in the interpretation and application of technical guidelines and requirements for product registration in order to reduce or obviate the need to duplicate the testing carried out during the research and development of new medicines. The objective of this harmonization is a more economical use of human, animal, and material resources, and the elimination of unnecessary delay in the global development and availability of new medicines while maintaining safeguards on quality, safety, and efficacy, and regulatory observations to protect public health.

- **Isolated Intermediate** – An intermediate that is obtained as the product after work-up of a reaction step in the synthetic scheme for the drug substance. The isolation or purification procedure should be part of the validated process. An aliquot of a reaction product that is worked-up and/or purified for purposes of characterization does not constitute an isolated intermediate.

- **Justification** – Reports containing scientific data and expert professional judgment to substantiate decisions (*SUPAC IR, Immediate Release Solid Oral Dosage Forms, Scale-up and Post-Approval Changes: Chemistry, Manufacturing and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation).*

- **Limit of Detection (LOD)** – The lowest amount of test material in a sample that can be detected but not necessarily quantified.

- **Limit of Quantitation (LOQ)** - The lowest amount of test material in a sample that can be quantitatively determined.

- **Linearity** – An analytical methods ability to obtain results that are directly proportional to the concentration of the test material in the sample.

- **List I Chemical** – A chemical specified by regulation of the Attorney General as a chemical that is used in manufacturing a controlled substance in violation of Title 21 USCS Section 812 and is important to the manufacture of the controlled substance.

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- **Listing Requirements** – All firms, unless exempted, are requested to list their commercially marketed drug products with FDA within 5 days after the beginning of operation. They are required to list/update their drug products listing twice a year.

- **Lot** - A batch, or a specific identified portion of a batch having uniform character and quality within specified limits. For an active pharmaceutical ingredient produced by continuous process, it is a specific identified amount produced in a unit of time or quantity in a manner that ensures its having uniform character and quality within specified limits.

- **Lot Number (Control Number or Batch Number)** – Any distinctive combination of letters, numbers, or symbols, or any combination of them, from which the complete history of the manufacture, processing, packing, holding, and distribution of a batch or lot of an active pharmaceutical ingredient or other material can be determined.

- **Manufacturing/Processing** – Repackaging or otherwise changing the container, wrapper, or labeling of any drug product package in the distribution process from the original producer to the ultimate consumer.

- **Manufacturing Information** – Information pertaining to the composition, manufacture, stability, and controls used for manufacturing the drug substance and drug product. This information is assessed to insure the company can adequately produce and supply consistent batches of the drug.

- **Method Validation** – The process of proving that an analytical test procedure is effective for its intended use.

- **New Molecular Entity** – The designated therapeutic moiety (active pharmaceutical ingredient) in a dosage form that has not been approved for marketing in the United States (also referred to as a new chemical entity or new drug substance). It may be a complex, simple ester, or salt of a previously approved active chemical ingredient.

- **Operational Qualification (OQ)** – The documented verification that the equipment and ancillary systems perform as intended throughout anticipated operating ranges (i.e., pressures, temperatures, times).

- **Performance Qualification** – The documented verification that the equipment and ancillary systems will function according to a specification appropriate to its routine use.

- **Pilot-Plant Scale** – The manufacture of either drug substance or drug product by a procedure fully representative of and simulating that to be applied on a full manufacturing scale.

- **Pilot Scale** – The manufacture of a bulk drug substance or intermediate on a reduced scale by processes representative of and simulating that to be applied on a larger, commercial manufacturing scale.

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- **Polymorphism** – The occurrence of different crystalline forms of the same drug substance (ICH Q3A). This may include solvation or hydration products (also known as pseudopolymorphs) and amorphous forms.

- **Precision** – The degree of agreement of individual test results when an analytical procedure is applied repeatedly to multiple samplings of a homogenous sample (usually expressed as a standard deviation).

- **Production Batch** – A batch of a drug substance or drug product manufactured at the scale typically encountered in a facility intended for marketing production.

- **Process Validation** – Establishing documented evidence that provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specification and quality characteristics.

- **Product Information Management Branch (FDA)** – Assists firms with mandatory updates of their drug product listings.

- **Prospective Validation** – Establishing documented evidence that a system does what it purports to do prior to the commercial distribution of a new active pharmaceutical ingredient or an existing active pharmaceutical ingredient made by a new or modified process.

- **Qualification** – The action of proving that any equipment or process works correctly and consistently and produces the expected results. Qualification is part of, but not limited to, a validation process, i.e., installation qualification (IQ), operational qualification (OQ), and performance qualification (PQ).

- **Quality** – The suitability of either a drug substance or drug product for its intended use. This term includes such attributes as the identity, strength, and purity of the article.

- **Quality Assurance** – The sum total of the organized activities performed with the intent to ensure that all active pharmaceutical ingredients are of the quality required for their intended use.

- **Quality Control Unit** – Any person or organizational element designated by the firm to be responsible for the duties relating to quality control.

- **Range** – The upper and lower limits (inclusively) of the test material for which an analytical method can perform with precision, accuracy, and linearity.

- **Raw material** – Any ingredient intended for use in the production of active pharmaceutical ingredients. These may include starting materials, process aids, solvents, and reagents.

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- **Reagent** – A substance, other than a starting material or solvent, that is used in the manufacture of a drug substance.

- **Reference Standard** – A particular lot or batch of drug substance specifically prepared, either by independent synthesis or by additional purification of production material, and shown, by an extensive set of analytical tests, to be authentic material of the highest purity reasonably attainable.

- **Registration Exemption** – Pharmacies, hospitals, and clinics that dispense drug product at retail; licensed physicians who use drug products solely for purposes related to their professional practice; and/or persons using drug products solely for their professional needs and are not for sale are exempt from registration.

- **Registration Process** – Firms can register with the FDA by obtaining a Registration of Drug Establishment Form within five days after the beginning of operation or submission of an application. Firms are required to re-register annually by returning an Annual Registration of Drug Establishment Form within 30 days after receiving it from the Product Information Management Branch.

- **Registration Requirements** – A firm must register all drug products (Domestic Manufacturers, Domestic Repackers, Domestic Labelers, and submissions for New Human Drug Application, New Animal Drug Application, Medicated Feed Application, Antibiotic Drug Application, and Establishment License Application to Manufacture Biological Products) whether or not they enter interstate commerce. All domestic distributors and foreign firms importing drug products into the United States must obtain a labeler code and list all of their products.

- **Reprocessing** – Introducing an intermediate or active pharmaceutical ingredient that does not conform to standards or specifications, back into the process and repeating one or more steps that are part of the established manufacturing process (e.g., recrystallization using the same solvent).

- **Retest Date (ICH Q1A)** – The date when samples of the drug substance should be reexamined to ensure that the material is still suitable for use.

- **Retest Period** – The period of time during which the active pharmaceutical ingredient can be considered to remain within specifications, and therefore acceptable for use in the manufacture of a given drug product, provided that it has been stored under defined conditions. After this period, the active pharmaceutical ingredient should be retested for compliance with specifications before use.

- **Retrospective Validation** – Establishing documented evidence that a system does what it purports to do based on a review and analysis of historic information. It is normally conducted on an active pharmaceutical ingredient already being commercially distributed and is based on accumulated production, testing, and control data.

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- **Reworking** – Subjecting an intermediate or active pharmaceutical ingredient that does not conform to standards or specifications to one or more processing steps that are different from the established manufacturing process (e.g., recrystallizing with a different solvent).

- **Ruggedness** – A measure of the lack of influence on test results of operational and environmental variables of an analytical method. Also defined as the degree of reproducibility of test results obtained by the analysis of the same samples under a variety of test conditions.

- **Schedule I Controlled Substance** – A drug or other substance which has a high potential for abuse, has no currently accepted medical use in treatment in the United States, and for which there is a lack of accepted safety for use of the drug or other substance under medical supervision.

- **Schedule II Controlled Substance** – A drug or other substance which has a high potential for abuse, has a currently accepted medical use in treatment in the United States or a currently accepted medical use with severe restrictions, and for which abuse of the drug or other substance may lead to severe psychological or physical dependence.

- **Schedule III Controlled Substance** – A drug or other substance which has a potential for abuse less than the drugs or other substances in Schedules I and II, has a currently accepted medical use in treatment in the United States, and for which abuse of the drug or other substance may lead to moderate or low physical dependence or high psychological dependence.

- **Schedule IV Controlled Substance** – A drug or other substance which has a low potential for abuse relative to the drugs or other substances in Schedule III, has a currently accepted medical use in treatment in the United States, and for which abuse of the drug or other substance may lead to limited physical dependence or psychological dependence relative to the drugs or other substances in Schedule III.

- **Schedule V Controlled Substance** – A drug or other substance which has a low potential for abuse relative to the drugs or other substances in Schedule IV, has a currently accepted medical use in treatment in the United States, and for which abuse of the drug or other substance may lead to limited physical dependence or psychological dependence relative to the drugs or other substances in Schedule IV.

- **Selectivity** – The ability of a testing procedure to measure a test material in the presence of additional components that may be present in the sample matrix which could potentially interfere with the analytical method.

- **Semisynthetic Drug Substance** – A drug substance produced by fermentation and synthesis or synthesized from a precursor or structural element of natural origin (e.g., a natural product of natural or plant origin).

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- **Shelf Life; Expiration Dating Period** – The time interval that a drug product is expected to remain within the approved shelf-life specification provided that it is stored under the conditions defined on the label in the proposed container and closure.

- **Solvent** – An inorganic or an organic liquid used as the vehicle for the preparation of solutions or suspensions in the synthesis of a new drug substance or the manufacture of a new drug product.

- **Specification** – A list of tests, references to analytical procedures, and appropriate acceptance criteria that are numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which a drug substance should conform to be considered acceptable for its intended use. *Conformance to specifications* means that the drug substance, when tested according to the listed analytical procedures, will meet the listed acceptance criteria. Specifications are binding quality standards that are agreed to between the appropriate governmental regulatory agency and the applicant (ICH draft guidance *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances*).

- **Specific Test** – A test that is considered to be applicable to particular new drug substances or particular new drug products depending on their specific properties and/or intended use.

- **Specified Impurity** – An identified or unidentified impurity that is selected for inclusion in the new drug substance or new drug product specification and is individually listed and limited in order to assure the quality of the new drug substance or new drug product.

- **Stability** – The capacity of a drug substance or a drug product to remain within specifications established to ensure its identity, strength, quality, and purity throughout the retest period or expiration dating period, as appropriate.

- **Stability–Indicating Methodology** – Validated quantitative analytical methods that can detect the changes with time in the chemical, physical, or microbiological properties of the drug substance and drug product, and that are specific so that the contents of active ingredient, degradation products, and other components of interest can be accurately measured without interference.

- **Starting Material** – A material used in the synthesis of a drug substance that is incorporated as an element into the structure of an intermediate and/or of the drug substance. Starting materials are usually available from commercial sources, and their chemical and physical properties, structure, and impurity profile are well defined in the chemical literature.

- **Testing** – A technical operation that consists of the determination of one or more characteristics or performance of a given product, material, equipment organism, physical phenomena, process, or service according to a specified procedure.

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- **Testing Requirements** – Test conditions and standard operating procedures with clear instructions describing how to perform the tests and how to evaluate the results.

- **Theoretical Yield** – The quantity that would be produced at any appropriate phase of manufacture, processing, or packing of a particular active pharmaceutical ingredient or intermediate, based upon the quantity of components to be used, in the absence of any loss or error in actual production.

- **Total Impurities** – The sum of all impurities observed above the limit of quantitation.

- **Unidentified Impurity** – An impurity that is defined solely by qualitative analytical properties (e.g. chromatographic retention time).

- **Universal Test** – A test that is considered to be potentially applicable to all new drug substances or all new drug products (e.g. appearance, identification, assay, and impurity tests).

- **Validation** – Establishing documented evidence that provides a high degree of assurance that a system, method, or operation does what it is supposed to do, reliably and consistently.

- **Validation Protocol** – A written plan stating how validation will be conducted and identifying specific acceptance criteria. For example, the protocol for a typical manufacturing process identifies processing equipment, critical process parameters/operating ranges, product characteristics, sampling and test data to be collected, number of validation runs, and acceptable test results.

- **Verification** – Confirmation by examination and provision of evidence that specified requirements have been met.

- **Warning Letter** – A written communication from FDA notifying an individual or firm that the agency considers one or more products, practices, processes, or other activities to be in violation of the Federal Food, Drug, and Cosmetic Act, or other Acts, and that failure of the responsible party to take appropriate and prompt action to correct and prevent any future repeat of the violation, may result in administrative and/or regulatory enforcement action without further notice.

- **Working Standard** – An active pharmaceutical ingredient, intermediate or other substance of established quality and purity, as shown by comparison to a primary reference standard, used as a reference for routine laboratory analysis.

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